UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/756,783	01/12/2004	Tania Watts	12973/1	3693

26646 7590 01/05/2007

KENYON & KENYON LLP
ONE BROADWAY
NEW YORK, NY 10004

EXAMINER	
OUSPENSKI, ILIA I	
ART UNIT	PAPER NUMBER
1644	

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
3 MONTHS	01/05/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Office Action Summary	Application No.	Applicant(s)	
	10/756,783	WATTS ET AL.	
	Examiner	Art Unit	
	ILIA OUSPENSKI	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *20 October 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-41* is/are pending in the application.

4a) Of the above claim(s) *1-22 and 27-37* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *23-26 and 38-41* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *12 January 2004* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *7/12/2004*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. Applicant's amendment and remarks, filed on 10/20/2006, are acknowledged.

Claims 1, 12, 23, 24, and 33 have been amended.
Claims 38 – 41 have been added.

Claims 1 – 41 are pending.

2. Applicant's election with traverse of Group II (claims 23 – 26, and newly added claims 38 – 41, drawn to an antigen presenting cell comprising a vector encoding 4-1BBL and B7 molecules, as well as a composition and a vaccine comprising said cell) in the reply filed on 10/20/2006 is acknowledged.

Applicant further elected the Species of B7.1 as the B7 molecule.

The traversal is on the grounds that a search of the entire application allegedly would not constitute an undue burden.

This is not found persuasive, for the reasons of record set forth in the previous Office Action. The various distinct ingredients, method steps, and endpoints of the claimed methods require separate and distinct searches. As such, it would be burdensome to search these Inventions together. Further, Applicant is reminded that if the elected product claims are subsequently found allowable, withdrawn process claims that depend from or otherwise include all the limitations of the allowable product claim will be rejoined in accordance with the provisions of MPEP § 821.04.

The requirement is still deemed proper and is therefore made FINAL.

Claims 1 – 22 and 27 – 37 are withdrawn from further consideration by the Examiner, under 37 C.F.R. § 1.142(b), as being drawn to nonelected inventions, there being no allowable generic or linking claim.

Claims 23 – 26 and 38 – 41 are under consideration in the instant application.

3. Applicant's claim for domestic priority under 35 U.S.C. §§ 119(e) and 120 is acknowledged.

However, the provisional application USSN 60/3044,430, and priority application PCT/CA02/01033 (published on 01/23/2003 as WO 03/006632, which document is being cited of record by the Examiner), fail to provide adequate support under 35 U.S.C. §112 for claims 23 – 26 and 38 – 41 of this application. Specifically, insufficient support was identified for the limitation of a human antigen presenting cells comprising, in addition to a vector encoding 4-1BBL, "a recombinant vector comprising a nucleic acid encoding a B7 molecule."

It is acknowledged that provisional applications USSN 60/3044,430 (page 18, lines 15 – 23) and PCT/CA02/01033 (page 47, lines 24 – 27 of WO 03/006632) mention "B7 family members" on contaminating APC cell. Furthermore, PCT/CA02/01033 reviews the knowledge in the art that binding of B7 molecules on antigen-presenting cells to CD28 receptors on T cells can provide a costimulatory signal (page 4, lines 1 – 3, and page 6, lines 7 – 9 of WO 03/006632). However, this disclosure is not deemed sufficient to provide adequate support under 35 U.S.C. §112 for the claimed limitations.

Consequently, claims 23 – 26 and 38 – 41 have been accorded the priority of the filing date of the instant application, i.e. 01/12/2004.

Should Applicant disagree with the Examiner's factual determination above, it is incumbent upon Applicant to provide a showing that specifically supports the instant claim limitations.

4. Applicant's IDS, filed 07/12/2004, is acknowledged, and has been considered.

5. The use of trademarks has been noted in this application (e.g. Ficoll-Paque on page 99, line 22). Each letter of the trademarks should be capitalized wherever it appears and be accompanied by the generic terminology. Although the use of trademarks is permissible in patent applications, the proprietary nature of the marks should be respected and every effort made to prevent their use in any manner which might adversely affect their validity as trademarks.

The disclosure is further objected to because it contains embedded hyperlinks and/or other form of browser-executable code, e.g. on pages 37 and 48. Applicant is required to delete the embedded hyperlink and/or other form of browser-executable code. See MPEP § 608.01. In addition, Applicant is requested to review the application for embedded hyperlinks and/or other forms of browser-executable code and delete them. Embedded hyperlinks and/or other form of browser-executable code are impermissible in the text of the application as they represent an improper incorporation by reference. See MPEP § 608.01(p).

6. The following is a quotation of the **second paragraph of 35 U.S.C. §112**.

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

7. Claims 38 and 39 are rejected under **35 U.S.C. §112, second paragraph**, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 38 and 39 are indefinite in the recitation of "said vector," because the recitation lacks proper antecedent basis in the base claim 23, which recites two separate vectors. Therefore, one of ordinary skill in the art would not be reasonably apprised of the metes and bounds of the claimed invention, specifically, which of the two vectors recited in claim 23 is a viral vector.

Applicant is reminded that any amendment must point to a basis in the specification so as not to add new matter. See MPEP §§ 714.02 and 2163.06.

8. The following is a quotation of the **first paragraph of 35 U.S.C. §112**:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

9. Claims 23 – 26 and 38 – 41 are rejected under **35 U.S.C. §112, first paragraph**, as failing to comply with the written description requirement. The claims contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention.

A. Applicant is not in possession of the claimed human antigen presenting cell, because Applicant is not in possession of "a nucleic acid" encoding a generically recited "4-1BBL."

The specification discloses at page 4, lines 21 – 22, that "the 4-1BB ligand" is termed 4-1BBL. Further, it is exemplified that "in an embodiment, the 4-1BBL is substantially identical to SEQ ID NO:2" (page 14, last paragraph), where "substantially identical" means that sequences "share at least about 50% sequence similarity or identity, or if the sequences share defined functional motifs" (page 47, lines 7 – 11). It is also disclosed that "non-limiting examples of 4-1BB ligands include fragments or variants of human 4-1BBL as well as primate homologs thereof, peptidomimetics thereof and the like, which retain their binding activity to human 4-1BB" (page 37 first paragraph). Therefore, when interpreted in light of the specification, the instant claims encompass a genus of polypeptides comprising, but not limited to, sequence variants and fragments of the disclosed sequence.

The instant claims do not provide sufficient structural and functional characteristics of the genus of polypeptides encompassed by the instant claim language, coupled with a known or disclosed correlation between function and structure. Consequently, the specification does not describe the claimed subject matter in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention.

The Guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, ¶ 1 "Written Description" Requirement make clear that the written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species by actual reduction to practice, reduction to drawings, or by disclosure of relevant, identifying characteristics, i.e., structure or other physical and/or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show the applicant was in possession of the genus (Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 2001, see especially page 1106 3rd column).

The specification discloses a single polypeptide of SEQ ID NO:2. The instant claims encompass in their breadth, without limitation, any polypeptide at least 50% identical, or any fragment or homolog of the sequence. However, in the absence of sufficient description of a representative number of species by actual reduction to practice, reduction to drawings, or by disclosure of relevant, identifying characteristics, the claimed invention is not described in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention.

Attwood (Science, 2000; 290: 471 – 473) teaches that "[i]t is presumptuous to make functional assignments merely on the basis of some degree of similarity between sequences. Similarly, Skolnick et al. (Trends in Biotech., 2000; 18: 34 – 39) teach that

the skilled artisan is well aware that assigning functional activities for any particular protein or protein family based upon sequence homology is inaccurate, in part because of the multifunctional nature of proteins (e.g., "Abstract" and "Sequence-based approaches to function prediction", page 34). Even in situations where there is some confidence of a similar overall structure between two proteins, only experimental research can confirm the artisan's best guess as to the function of the structurally related protein (see in particular "Abstract" and Box 2).

Further, the specification does not appear to have provided sufficient written description of functional fragments of 4-1BBL, specifically with regard to which subsequences of SEQ ID NO:2 would share the activity of SEQ ID NO:2. Neither does the specification appear to have provided sufficient description of a representative number of species by actual reduction to practice, reduction to drawings, or by disclosure of relevant, identifying characteristics.

Therefore, Applicant is not in possession of a generically recited "4-1BB," and thus of the claimed human antigen presenting cell.

B. Applicant is not in possession of the claimed human antigen presenting cell, because Applicant is not in possession of "a nucleic acid" encoding a generically recited "B7 molecule."

The instant specification discloses two examples of B7 molecules: B7.1 and B7.2 (e.g. page 15, lines 1 – 12). However, a skilled artisan at the time the invention was made was aware that the family of B7 molecules included other members, such as e.g. B7-H3 and B7x, as reviewed e.g. by Loke et al. (Arthritis Research and Therapy, 2004, 6: 208 – 214; see entire document, in particular, e.g. the Abstract). The instant disclosure does not provide a representative description of the structural and functional properties a polypeptide must possess to fall within the scope of the instant claims, as encompassed by the generic recitation of "B7 molecule." Therefore, the skilled artisan cannot envision all the contemplated "B7 molecules" encompassed by the instant claims.

Furthermore, the instant specification discloses that B7.1, in one embodiment, is "substantially identical to SEQ ID NO:4," and B7.2, in one embodiment, is "substantially identical to SEQ ID NO:6" (page 15, lines 1 – 12), where "substantially identical" means that sequences "share at least about 50% sequence similarity or identity, or if the sequences share defined functional motifs" (page 47, lines 7 – 11). Therefore, when interpreted in light of the specification, the instant claims encompass a genus of polypeptides comprising, but not limited to, sequence variants which may be up to 50% different from the disclosed sequences.

The specification discloses two polypeptides of SEQ ID NOS: 4 and 6, while the instant claims encompass in their breadth any polypeptide at least 50% identical to these sequences. However, in the absence of sufficient description of a representative number of species by actual reduction to practice, reduction to drawings, or by disclosure of relevant, identifying characteristics, the claimed invention is not described in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention. Metzler et al. (Nature Structural Biol. 1997; 4: 527 – 531) show that any of a variety of single amino acid changes can alter or abolish the ability of CTLA4 to interact with its ligands B7-1 and B7-2 (also known as CD80 and CD86; e.g., summarized in Table 2).

These references demonstrate that even a single amino acid substitution or what appears to be an inconsequential chemical modification will often dramatically affect the biological activity and characteristic of a protein. Thus, the specification fails to provide a sufficient written description as to which modifications of the disclosed sequence can be tolerated that will allow the protein to function as claimed.

Vas-Cath Inc. v. Mahurkar, 19 USPQ2d 1111, makes clear that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The invention is, for purposes of the written description inquiry, whatever is now claimed." (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See Vas-Cath at page 1116.). Consequently, Applicant was not in possession of the instant claimed invention. See University of California v. Eli Lilly and Co. 43 USPQ2d 1398.

Applicant is directed to the final Guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, ¶ 1 "Written Description" Requirement, Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 2001.

10. Claim 26 is rejected under **35 U.S.C. §112, first paragraph**, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention.

The specification does not provide a sufficient enabling description of the claimed "vaccine" comprising the recited antigen presenting cell.

A skilled artisan at the time the invention was made was aware that a "vaccine" is a composition which has a prophylactic or therapeutic effect *in vivo*, i.e. the claimed antigen presenting cells must possess the properties of a prophylactically or therapeutically effective adjuvant.

Factors to be considered in determining whether undue experimentation is required to practice the claimed invention are summarized in In re Wands (858 F2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988)). The factors most relevant to this rejection are the scope of the claim, the amount of direction or guidance provided, limited working examples, the unpredictability in the art and the amount of experimentation required to enable one of skill in the art to practice the claimed invention.

The instant specification discloses at pages 105 – 108 working examples showing that the antigen-presenting cells of the invention are capable of enhancing T cell expansion *in vitro*. However, it is highly unpredictable how the results of *in vitro* experiments would translate into *in vivo* activity. Fore example, Singh et al. (Nature Biotechnology, 1999, 17: 1075 – 1081; see entire document) review that many experimental adjuvants that appear effective *in vitro* or even those that progress to clinical trials, have proven too toxic or ineffective in clinical use (see entire document, in particular, e.g. the abstract, and page 1075, second column, first paragraph). Therefore, an unreasonably extensive amount of experimentation would be required to enable the skilled artisan to produce a "vaccine" comprising the claimed cells. Given the scope of the claims, limited working examples, the unpredictability in the art and the amount of experimentation required; the amount of direction or guidance provided in the instant specification is not seen as sufficient to enable one of skill in the art to make and use the claimed invention, i.e. to produce a "vaccine" which has a prophylactic or therapeutic effect, because it is unpredictable whether the claimed antigen-presenting cells are usable as a prophylactically or therapeutically effective vaccine *in vivo*. Therefore, it would take undue trials and errors to make and use the claimed invention.

11. The following is a quotation of the appropriate paragraphs of **35 U.S.C. §102** that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless --

(a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

12. Claims 23 – 26 and 38 – 41 are rejected under **35 U.S.C. §102(a)** as being anticipated by Chen et al. (WO 03/049755; published 06/19/2003; see entire document).

It is noted that the instant claims have been accorded the priority of the filing date of the instant application, i.e. 01/12/2004 (see section 3 above).

Chen et al. teach APC (antigen-presenting cells) which can be used as an immunogenic stimulus, wherein the antigen-presenting cells express a recombinant agonistic 4-1BB-binding agent, and one or more of recombinant costimulatory molecules, such as B7.1 or B7.2 (see entire document, in particular, e.g. page 28, lines 16 – 22). Chen et al. teach that an agonistic agent that binds to the 4-1BB molecule can be the 4-1BB ligand (e.g. page 13, lines 9 – 19), i.e. 4-1BBL. Chen et al. further teach that the cells expressing these recombinant molecules will have been transformed or transfected with one or more nucleic acids comprised in expression vectors encoding these molecules. Chen et al. further teach that APCs may be obtained from a subject, transfected with the polynucleotides encoding the above polypeptides, and exposed to antigens or antigenic peptides (e.g. pages 31 – 32, bridging paragraph), i.e. loaded with these antigens. Elsewhere Chen et al. teach that the subjects from which the cells are obtained may be human (e.g. page 27, lines 3 – 5), i.e. the APCs of Chen et al. may be human. Therefore, when viewed for all they teach, Chen et al. disclose a human antigen-presenting cell comprising a recombinant vector comprising a nucleic acid encoding 4-1BB ligand (i.e. 4-1BBL), a recombinant vector comprising a nucleic acid

encoding a B7 molecule (B7.1 or B7.2), and an antigen. As such, the teachings of Chen et al. anticipate the instant claim 23.

Claim 24 is anticipated, because Chen et al. teach that the nucleic acid encoding the immunogenic stimulus (i.e. a B7 molecule) and the nucleic acid encoding the 4-1BB binding agent (i.e. 4-1BBL) can be in the same nucleic acid molecule (e.g. claim 31), i.e. in the same vector.

Claim 25 is anticipated, because Chen et al. teach the recombinant cells of the invention can be suspended in a pharmaceutically acceptable carrier (e.g. page 27, lines 16 – 18).

Claim 26 is anticipated, because Chen et al. specifically refer to the cells of the invention as a "vaccine" (e.g. Example 6 at pages 47 – 48).

Claim 38 is anticipated, because Chen et al. teach that the transfection step can be accomplished by viral infection (e.g. page 32, lines 14 – 16), i.e. using a viral vector.

Claim 39 is anticipated, because Chen et al. teach that suitable expression vectors include viral vectors such as adenoviruses (e.g. page 30, lines 7 – 9).

Claim 40 is anticipated, because Chen et al. teach that the antigen may be a peptide, and may be from an infectious microorganism (e.g. page 31, lines 25 – 26), wherein the infectious microorganism may be a virus (e.g. claim 8).

Claim 41 is anticipated, because Chen et al. teach that costimulatory molecules of the invention which can be combined with 4-1BBL include B7.1 and B7.2 (e.g. page 28, lines 16 – 22).

Therefore, the reference teachings anticipate the instant claimed invention.

13. Conclusion: no claim is allowed.

14. Any inquiry concerning this communication or earlier communications from the examiner should be directed to ILIA OUSPENSKI whose telephone number is 571-272-2920. The examiner can normally be reached on Monday-Friday 9 - 5.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on 571-272-0841. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

ILIA OUSPENSKI, Ph.D.
Patent Examiner
Art Unit 1644

December 23, 2006